

Our Ref.: 427.010-1-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: :
Dennis BIGG et al :
Serial No.: :
Filed: Concurrently Herewith :
For: NEW...CONTAINING THEM :
600 Third Avenue
New York, NY 10016
February 4, 2002

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE SPECIFICATION:

Page 1, before line 1, insert

--PRIOR APPLICATIONS

This application is a Continuation-in-Part of U.S. Patent Application Serial No. 09/332,520 filed June 14, 1999 which is a Continuation-in-Part of U.S. Patent Application Serial No. 973,561 filed December 2, 1997, now U.S. Patent No. 5,981,542 which is a 371 of PCT/FR96/00980 filed June 21, 1996 and a Continuation-in-Part of U.S. Patent Application Serial No. 09/806,952 filed April 5, 2001 which is a 371 of PCT/FR00/00461 filed February 24, 2000.--

nitro, lower nitroalkyl, amido, lower amidoalkyl, hydrazino, lower hydrazinoalkyl, azido, lower azidoalkyl, lower alkyl lower sulphonylalkyl, $-(CH_2)_mNZ'_6Z'_7$, $-(CH_2)_mOZ'_6$, $-(CH_2)_mSZ'_6$, $-(CH_2)_mCO_2Z'_6$, $-(CH_2)_mCO_2Z'_6$, $-(CH_2)_mNZ'_6C(O)Z_8$, $-(CH_2)_mC(O)Z_8$, $-(CH_2)_mOC(O)Z_8$, $-O-(CH_2)_mNZ'_6Z'_7$, $-OC(O)NZ'_6Z'_7$, $-OC(O)(CH_2)_mCO_2Z'_6$, $-OSO_2Z_7$, $-(CH_2)_mN(CH_3)(CH_2)_nNZ'_6Z'_7$, $-(CH_2)_mOC(O)NZ'_6Z'_7$, $-(CH_2)_mS(O)_qZ_{11}$, $-(CH_2)_mP(O)Z_{12}Z_{13}$, $-(CH_2)_2P(S)Z_{12}Z_{13}$, $-(CH_2)_mSiZ'_{11}Z'_{12}Z'_{13}$; or ii) $-(CH_2)_n[N=X]$, $-OC(O)[N=X]$, $-(CH_2)_mOC(O)[N=X]$, aryl and lower arylalkyl, each unsubstituted or substituted with 1 to 4 members on the aryl or the heterocycle selected from the group consisting of lower alkyl, lower arylalkyl, halo, hydroxy, $-OCF_3$, nitro, amino, lower alkylamino, di(lower alkyl)amino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl or iii) Z_3 and Z_4 or Z_4 and Z_5 form together a chain of 3 or 4 members in which the elements of the chain are selected from the group consisting of CH, CH_2 , O, S, N or NZ_9 ;

Z_7

is a member selected from the group consisting of lower alkyl unsubstituted or substituted by at least one halo, aryl, aryl unsubstituted or substituted by at least one lower alkyl;

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Z'₆ and Z'₇ are independently a member selected from the group consisting of i) H, lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl and haloalkyl, or ii) aryl or lower arylalkyl, unsubstituted or substituted on the aryl with 1 to 4 members selected from the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl;

Z₈ is a member selected from the group consisting of i) H, lower alkyl, lower hydroxyalkyl, amino, lower alkylamino, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy, lower alkoxy lower alkyl and lower haloalkyl, or ii) aryl or lower arylalkyl unsubstituted or substituted on the aryl with 1 to 4 members selected from the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl;

Z₉ is a member selected from the group consisting of

i) H, lower alkyl, lower haloalkyl, or ii) aryl and lower arylalkyl unsubstituted or substituted with a member selected from the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxalkyl, lower alkoxy and lower alkoxy lower alkyl;

Z_{10} is a member selected from the group consisting of i) H, lower alkyl, lower haloalkyl and lower alkoxy, or ii) aryl unsubstituted or substituted on the aryl with a member selected from the group consisting of lower alkyl, lower haloalkyl, lower hydroxyalkyl and lower alkoxy lower alkyl;

Z_{11} is a member selected from the group consisting of lower alkyl, aryl, $-(CH_2)_mOZ_{14}$, $-(CH_2)_mSZ_{14}$, $-(CH_2)_2NZ_{14}Z_{15}$ and $(CH_2)_m[N=X]$;

Z_{12} and Z_{13} are independently members selected from the group consisting of lower alkyl, aryl, lower alkoxy, aryloxy and amino;

Z'_{11} , Z'_{12} and Z'_{13} are independently a member selected from the group consisting of H or lower alkyl;

Z_{14} and Z_{15} are independently a member selected from the group

consisting of H, lower alkyl and aryl;

Z_{16} is H or $-OZ_{21}$;

Z_{17} is $-OZ'_6$ or $-NZ'_6$ or $-NZ'_6Z'_7$;

Z_{18} and Z_{19} are independently a member selected from the group consisting of H, halo, lower alkyl, lower alkoxy and hydroxy;

Z_{20} is H or halo;

Z_{21} is a member selected from the group consisting of H, lower alkyl, $-CHO$ and $-C(O)(CH_2)_mCH_3$;

Z_p is a member selected from the group consisting of H or an easily cleavable group preferably chosen from the groups corresponding to the formula $-C(O)-A-NZ_{22}Z_{23}$, in which A represents a linear or branched alkylene unsubstituted or substituted by a member selected from the group consisting of free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino, mono and dialkylamino;

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Z_{22} and Z_{23} are independently a member selected from the group consisting of i) H, lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl, lower haloalkyl, or ii) aryl or lower arylalkyl unsubstituted or substituted on the aryl with 1 to 4 members selected from the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl;

m is an integer between 0 and 6;

n is 1 or 2; and

q is an integer from 0 to 2; and

[N=X] is a heterocyclic group with 4 to 7 ring members with the nitrogen atom which a member of the heterocyclic ring, and X is the chain necessary to complete said heterocyclic group and selected from the group consisting of O, S, CH_2 , CH, N, NZ_9 , and $C(O)Z_{10}$;

and its pharmaceutically acceptable salt.

Claim 2 (amended) A compound of claim 1, in racemic or enantiomeric form or any combinations of these forms, wherein

Z_1 is a member selected from the group consisting of lower alkyl, lower alkenyl, lower alkynyl, lower haloalkyl, lower alkoxy lower alkyl and lower alkylthio lower alkyl;

Z_2 is a member selected from the group consisting of H, halo and $-\text{OSO}_2Z_7$;

Z_3, Z_4 and Z_5 are independently a member selected from the group consisting of i) H, halo, lower haloalkyl, lower alkyl, lower alkenyl, cyano, lower cyanoalkyl, nitro, lower nitroalkyl, amido, lower amidoalkyl, hydrazino, lower hydrazinoalkyl, azido, lower azidoalkyl, $-(\text{CH}_2)_m\text{NZ}'_6\text{Z}'_7$, $-(\text{CH}_2)_m\text{OZ}'_6$, $-(\text{CH}_2)_m\text{SZ}'_6$, $-(\text{CH}_2)_m\text{CO}_2\text{Z}'_6$, $-(\text{CH}_2)_m\text{NZ}'_6\text{C}(\text{O})Z_8$, $-(\text{CH}_2)_m\text{C}(\text{O})Z_8$, $-(\text{CH}_2)_m\text{OC}(\text{O})Z_8$, $-\text{O}(\text{CH}_2)_m\text{NZ}'_6\text{Z}'_7$, $-\text{OC}(\text{O})\text{NZ}'_6\text{Z}'_7$, $-\text{OC}(\text{O})(\text{CH}_2)_m\text{CO}_2\text{Z}'_6$ and $-\text{OSO}_2Z_7$ or ii) $-(\text{CH}_2)_n[\text{N}=\text{X}]$, $-\text{OC}(\text{O})[\text{N}=\text{X}]$, $-(\text{CH}_2)_m\text{OC}(\text{O})[\text{N}=\text{X}]$ wherein $[\text{N}=\text{X}]$ is a heterocyclic group with 4 to 7 ring members with the nitrogen atom, which is a member of the heterocyclic group, and X is the remaining members, which are necessary to complete the heterocyclic group, selected from the group consisting of O, S,

CH_2 , CH , N , NZ_9 and COZ_{10} , aryl or lower arylalkyl, unsubstituted or substituted on the aryl or the heterocycle with 1 to 4 members selected from the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl or iii) Z_3 and Z_4 or Z_4 and Z_5 form together a chain with 3 or 4 members in which the elements of the chain are selected from the group consisting of CH , CH_2 , O , S , N and NZ_9 ;

Z_6

is a member selected from the group consisting of i) H , halo, lower haloalkyl, alkyl containing 1 to 12 carbon atoms unsubstituted or substituted by at least one halo, lower alkoxy, lower alkoxy lower alkyl, lower alkylthio lower alkyl, cycloalkyl, cycloalkyl lower alkyl, cyano, cyanoalkyl, lower alkyl lower sulphonylalkyl, lower hydroxyalkyl, nitro, $-(\text{CH}_2)_m\text{C}(\text{O})\text{Z}_8$, $-(\text{CH}_2)_m\text{NZ}'_6\text{C}(\text{O})\text{Z}_8$,

$-(\text{CH}_2)_m\text{NZ}'_6\text{Z}'_7$, $-(\text{CH}_2)_m\text{N}(\text{CH}_3)(\text{CH}_2)_n\text{NZ}'_6\text{Z}'_7$,

$-(\text{CH}_2)_m\text{OC}(\text{O})\text{Z}_8$, $-(\text{CH}_2)_m\text{OC}(\text{O})\text{NZ}'_6\text{Z}'_7$, $-(\text{CH}_2)_m\text{S}(\text{O})_q\text{Z}_{11}$,

$-(\text{CH}_2)_m\text{P}(\text{O})\text{Z}_{12}\text{Z}_{13}$, $-(\text{CH}_2)_2\text{P}(\text{S})\text{Z}_{12}\text{Z}_{13}$, and

$-(\text{CH}_2)_m\text{SiZ}'_{11}\text{Z}'_{12}\text{Z}'_{13}$; or ii) $-(\text{CH}_2)_n[\text{N}=\text{X}]$, $-\text{OC}(\text{O})[\text{N}=\text{X}]$,

$-(\text{CH}_2)_m\text{OC}(\text{O})[\text{N}=\text{X}]$, each unsubstituted or unsubstituted on the heteroaryl with 1 to 4 members of the group consisting of lower alkyl, lower

arylalkyl, halo, hydroxy, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl; or iii) aryl or lower arylalkyl, each unsubstituted or substituted on the aryl with 1 to 4 members of the group consisting of lower alkyl, halo, hydroxy, nitro, $-OCF_3$, amino, lower alkylamino, di(lower alkyl)amino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl;

Z_7 is a member selected from the group consisting of lower alkyl unsubstituted or substituted by at least one halo, or unsubstituted or substituted by at least one lower alkyl;

Z'_6 and Z'_7 are independently a member selected from the group consisting of i) H, lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl and lower haloalkyl, or ii) aryl or lower arylalkyl unsubstituted or substituted on the aryl with 1 to 4 members of the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl;

Z₈

is a member selected from the group consisting of
i) H, lower alkyl, lower hydroxyalkyl, amino, lower
alkylamino, lower alkyl lower aminoalkyl, lower
aminoalkyl cycloalkyl, cycloalkyl lower alkyl,
lower alkenyl, lower alkoxy, lower alkoxy lower
alkyl and lower haloalkyl, or ii) aryl or lower
arylalkyl unsubstituted or substituted on the aryl
with 1 to 4 members of the group consisting of
lower alkyl, halo, nitro, amino, lower alkylamino,
lower haloalkyl, lower hydroxyalkyl, lower alkoxy
and lower alkoxy lower alkyl;

Z₉

is a member selected from the group consisting of
i) H, lower alkyl and lower haloalkyl, or ii) aryl
or lower arylalkyl unsubstituted or substituted
with a member of the group consisting of lower
alkyl, halo, nitro, amino, lower alkylamino, lower
haloalkyl, lower hydroxyalkyl, lower alkoxy and
lower alkoxy lower alkyl;

Z₁₀

is a member selected from the group consisting of
i) H, lower alkyl, lower haloalkyl and lower
alkoxy, or ii) aryl unsubstituted or substituted on
the aryl with 1 to 4 members of the group
consisting of lower alkyl, lower haloalkyl, lower
hydroxyalkyl and lower alkoxy lower alkyl;

Z_{11} is a member selected from the group consisting of lower alkyl, aryl, $-(CH_2)_mOZ_{14}$, $-(CH_2)_mSZ_{14}$, $-(CH_2)_2NZ_{14}Z_{15}$ and $-(CH_2)_m[N=X]$;

Z_{12} and Z_{13} are independently a member selected from the group consisting of lower alkyl, aryl, lower alkoxy, aryloxy and amino;

Z'_{11} , Z'_{12} and Z'_{13} are independently H or lower alkyl;

Z_{14} and Z_{15} are independently a member selected from the group consisting of H, lower alkyl and aryl;

Z_{16} is H or $-OZ_{21}$;

Z_{17} is OZ'_6 or $-NZ'_6Z'_7$;

Z_{18} and Z_{19} are independently a member selected from the group consisting of H, halo, lower alkyl, lower alkoxy and hydroxy;

Z_{20} is H or halo;

Z_{21} is a member selected from the group consisting of H, lower alkyl, $-CHO$ and $-C(O)(CH_2)_mCH_3$;

Z_p represents H or an easily cleavable group of the formula $-C(O)-A-NZ_{22}Z_{23}$, wherein A is alkylene unsubstituted or substituted by a member selected from the group consisting of free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino and mono and dialkylamino;

Z_{22} and Z_{23} are independently a member selected from the group consisting of i) H, lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl, lower haloalkyl, or ii) aryl or lower arylalkyl unsubstituted or substituted by 1 to 4 members of the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl;

m is an integer between 0 and 6; and

n is 1 or 2; and

q is an integer from 0 to 2; and

[N=X] is a heterocyclic group with 4 to 7 ring members

with the nitrogen atom which is a member of the heterocyclic ring, and X is the chain necessary to complete said heterocyclic group and is selected from the group consisting of O, S, CH₂, CH, N, NZ₉ and COZ₁₀;

and a pharmaceutically acceptable salt thereof.

Claim 3 (amended) A compound of claim 1 wherein Z₂ is H or halo and pharmaceutically acceptable salt thereof.

Claim 4 (amended) A compound of claim 1 wherein Z₃ is halo; and a pharmaceutically acceptable salt thereof.

Claim 5 (amended) A compound of claim 1 wherein

Z₁ is lower alkyl;

Z₂ is H or halo;

Z₃, Z₄ and Z₅ are independently a member selected from the group consisting of i) H, halo, lower alkyl, -(CH₂)_mNZ'₆Z'₇, -(CH₂)_mOZ'₆ and -OSO₂Z₇ or ii) -(CH₂)_n[N=X] or iii) Z₃ and Z₄ or Z₄ and Z₅ form together a chain with 3 or 4 members in which the elements of the chain are selected from the group

consisting of CH, CH₂, O, S, N and NZ₉;

Z₆ is a member selected from the group consisting of
i) H, halo, alkyl of 1 to 12 carbon atoms unsubstituted or substituted by at least one halo, lower alkoxy lower alkyl, cycloalkyl, cycloalkyl lower alkyl, lower hydroxyalkyl, -(CH₂)_mNZ'₆Z'₇ and -(CH₂)_mSiZ'₁₁Z'₁₂Z'₁₃; or ii) -(CH₂)_n[N=X] unsubstituted or substituted with lower alkyl or lower arylalkyl or iii) aryl or lower arylalkyl unsubstituted or substituted with a member selected from the group consisting of lower alkyl, halo, -OCF₃, di(lower alkyl)amino and lower haloalkyl;

Z₇ is lower alkyl unsubstituted or substituted by at least one halo;

Z'₆ and Z'₇ are independently i) H, or lower alkyl, or ii) lower arylalkyl;

Z₉ is lower alkyl or lower arylalkyl;

Z'₁₁, Z'₁₂ and Z'₁₃ are independently lower alkyl;

Z₁₆ is H or -OZ₂₁;

Z_{17} is $-OZ'_6$ or $-NZ'_6Z'_7$;

Z_{18} and Z_{19} are independently H or halo;

Z_{20} is H;

Z_{21} is a member selected from the group consisting of H, lower alkyl or $-C(O)(CH_2)_mCH_3$;

Z_p is H or $-C(O)-A-N_{22}Z_{23}$, in which A is alkylene unsubstituted or substituted by a member selected from the group consisting of free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino and mono and dialkylamino radicals;

Z_{22} and Z_{23} are independently H or lower alkyl;

m is an integer between 0 and 6;

n is 1 or 2; and

q is an integer from 0 to 2; and

$[N=X]$ is a heterocyclic group with 4 to 7 ring members, X is the chain necessary to complete said

heterocyclic group and is selected from the group consisting of O, CH₂, CH, N and NZ₉;

and a pharmaceutically acceptable salt thereof.

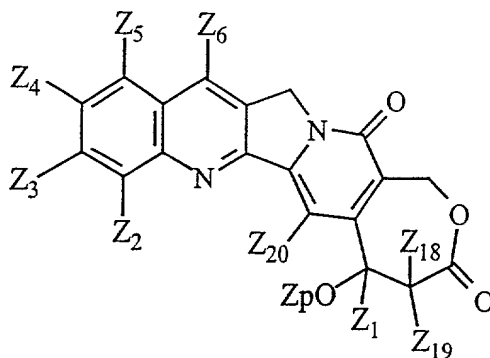
Claim 6 (amended) A compound of claim 1 wherein Z₁₈, Z₁₉ and Z₂₀ are H; and a pharmaceutically acceptable salt thereof.

Claim 7 (amended) A compound of claim 1 wherein Z₁ is ethyl and a pharmaceutically acceptable salt thereof.

Claim 8 (amended) A compound of claim 1 wherein Z_p is -C(O)-A-NZ₂₂Z₂₃ and a pharmaceutically acceptable salt thereof.

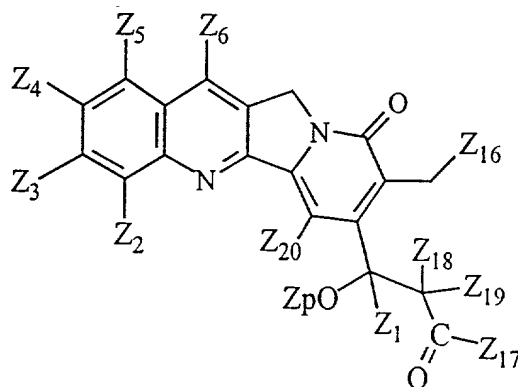
Claim 9 (amended) A compound of claim 1 wherein Z_p is H and a pharmaceutically acceptable salt thereof.

Claim 10 (amended) A compound of claim 1 having the formula



wherein Z_1 , Z_2 , Z_3 , Z_4 , Z_5 , Z_6 , Z_{18} , Z_{19} , Z_{20} and Z_p are as defined in claim 1 and a pharmaceutically acceptable salt thereof.

Claim 11 (amended) A compound of claim 1 having the formula



wherein Z_1 , Z_2 , Z_3 , Z_4 , Z_5 , Z_6 , Z_{16} , Z_{17} , Z_{18} , Z_{19} , Z_{20} and Z_p are as defined in claim 1 and a pharmaceutically acceptable salt thereof.

Claim 12 (amended) A compound of claim 1 wherein Z_6 is $-(CH_2)_mSiZ'_{11}Z'_{12}Z'_{13}$ and a pharmaceutically acceptable salt thereof.

Claim 13 (amended) A compound of claim 1 selected from the group consisting of:

(5R)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1H,3H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione; and

(5R)-5-ethyl-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-

tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

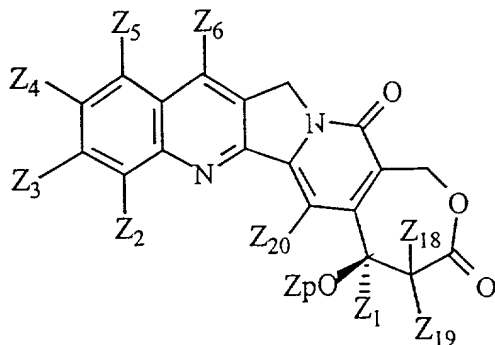
Claim 14 (amended) A compound of claim 1 wherein Z₂ is H or halo, Z₃ is halo, Z₄ is a member selected from the group consisting of H, halo and lower alkyl, Z₅ is H or halo, and Z₆ is a member selected from the group consisting of H, lower alkyl and -(CH₂)_n[N=X] substituted with lower alkyl and a pharmaceutically acceptable salt thereof.

Claim 15 (amended) A compound of claim 1 selected from the group consisting of:

(5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxpino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione; and

(5*R*-5-ethyl-9,11-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3,4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione; and a pharmaceutically acceptable salt thereof.

Claim 16 (amended) A compound of claim 1 having the formula



wherein Z_1 , Z_2 , Z_3 , Z_4 , Z_5 , Z_6 , Z_{18} , Z_{19} , Z_{20} and Z_p are as defined in claim 1 and a pharmaceutically acceptable salt thereof.

Claim 22 (amended) A method of treating cancer as claimed in claim 17, wherein the cancer is selected from the group consisting of leukemia, colon cancer, lung cancer, prostate cancer, breast cancer, melanoma, ovarian cancer and gastric cancer.

Claim 23 (amended) A method of treating cancer as claimed in claim 22, wherein the cancer is selected from the group consisting of leukemia, colon cancer, lung cancer, prostate cancer and breast cancer.

Claim 24 (amended) A method of claim 17 wherein R_{18} and R_{19} are hydrogen.

Claim 25 (amended) A method of claim 17 wherein R_p is hydrogen.

Claim 26 (amended) A method of claim 17 wherein R_1 is ethyl.

Claim 27 (amended) A method of claim 17 wherein the camptothecin analog is selected from the group consisting of:

(5R)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1H,3H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione;

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(5R)-1-[9-chloro-5-ethyl-5-hydroxy-10-methyl-3,15-dioxo-4,5,13,15-tetrahydro-1H,3H-oxepino[3',4:6,7]indolizino[1,2-b]quinolin-12-yl-methyl]-4-methyl-hexahdropyridium chloride;


(5R)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1H,3H-oxepino[3'4':6,7]indolizino[1,2-b]quinoline-3,15-dione; and

(5R)-5-ethyl-9,11-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1H,3H-oxepino[3'4':6,7]indolizino[1,2-b]quinoline-3,15-dione; and a pharmaceutically acceptable salt thereof.

REMARKS

The amendment is submitted to insert reference to the parent applications and their status, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS


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Attorney for Applicant(s)
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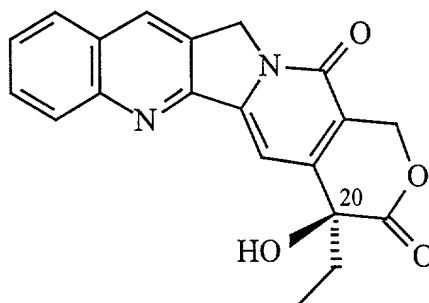
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MARKED-UP VERSION OF SPECIFICATION

New analogues of camptothecin,
their use as medicaments and
the pharmaceutical compositions containing them

See insert "A"

Camptothecin is a natural compound which has been isolated for the first time from
 5 the leaves and the bark of the Chinese plant called *camptotheca acuminata* (see Wall
 et al. J. Amer. Chem. Soc. 88:3888 (1966)). Camptothecin is a pentacyclic compound
 constituted by an indolizino[1,2-b]quinoline fragment fused with an α -hydroxylactone
 with six members. The carbon in position 20 which carries the α -hydroxy group is
 10 asymmetrical and confers a rotatory power on the molecule. The natural form of
 camptothecin has an absolute "S" configuration as regards the carbon 20 and
 corresponds to the following formula:



Camptothecin has an anti-proliferative activity in several cancerous cell lines,
 including the cell lines of human tumors of the colon, lung and breast (Suffness, M et
 15 al: The Alkaloids Chemistry and Pharmacology, Bross A., ed., Vol. 25, p. 73
 (Academic Press, 1985)). It is suggested that the anti-proliferative activity of
 camptothecin is related to its inhibitory activity on DNA topoisomerase I.

It has been indicated that α -hydroxylactone was an absolute requirement both for the
in vivo and *in vitro* activity of camptothecin (Camptothecins: New Anticancer
 20 Agents, Putmesil, M et al, ed., p. 27 (CRC Press, 1995); Wall M. et al, Cancer Res.
 55:753 (1995); Hertzberg et al, J. Med. Chem. 32:715 (1982) and Crow et al, J. Med.
 Chem. 35:4160 (1992)). The present invention relates to a new class of compounds of
 camptothecin, in which a β -hydroxylactone replaces the natural α -hydroxylactone of
 camptothecin. The compounds according to the present invention present a powerful
 25 biological activity which is unexpected with regard to the state of the prior art.

Therefore a subject of the invention is new analogues of camptothecin which differ
 from all known derivatives of camptothecin in the sense that they contain β -
 hydroxylactone (or its open hydroxycarboxylic form) instead of an α -hydroxylactone
 (or its open hydroxycarboxylic form); or a pharmaceutically acceptable salt of one of

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INSERT "A"

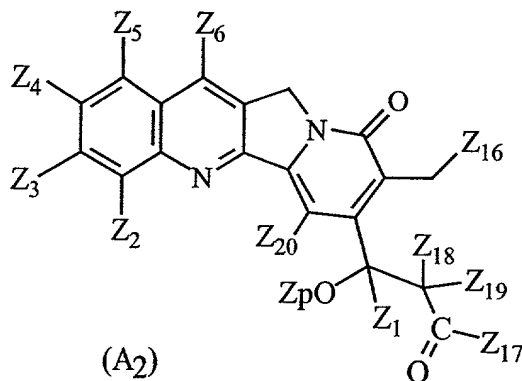
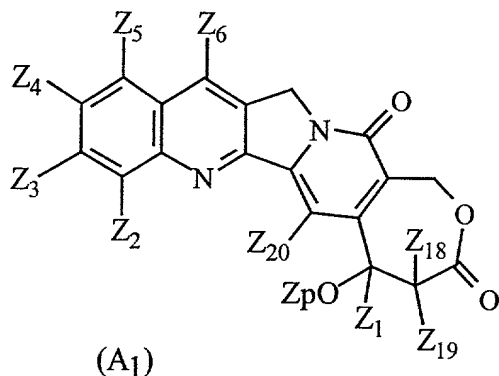
--PRIOR APPLICATIONS

This application is a Continuation-in-Part of U.S. Patent Application Serial No. 09/332,520 filed June 14, 1999 which is a Continuation-in-Part of U.S. Patent Application Serial No. 973,561 filed December 2, 1997, now U.S. Patent No. 5,981,542 which is a 371 of PCT/FR96/00980 filed June 21, 1996 and a Continuation-in-Part of U.S. Patent Application Serial No. 09/806,952 filed April 5, 2001 which is a 371 of PCT/FR00/00461 filed February 24, 2000.--

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MARKED-UP VERSION OF
CLAIMS

1. ~~Compounds of general formula (A₁) or (A₂)~~



in racemic or enantiomeric form or any combinations of these forms, ~~in which~~ *when*

Z₁ is (A) ~~represents a lower alkyl, a lower alkenyl, a lower alkynyl, a lower~~
haloalkyl, a lower alkoxy lower alkyl ^{and} or lower alkylthio lower alkyl;

Z_2, Z_3, Z_4, Z_5 and Z_6 ^{are} ~~represent~~, independently, (A)

i) H, halo, lower haloalkyl, alkyl containing 1 to 12 carbon atoms ^{or} optionally substituted by ^{it is} one or more halo radicals identical or different, lower alkenyl, cycloalkyl, cycloalkyl lower alkyl, cyano,

different, lower alkenyl, cycloalkyl, cycloalkyl lower alkyl, cyano, lower cyanoalkyl, nitro, lower nitroalkyl, amido, lower amidoalkyl, hydrazino, lower hydrazinoalkyl, azido, lower azidoalkyl, lower alkyl lower sulphonylalkyl, $-(CH_2)_mNZ'_6Z'_7$, $-(CH_2)_mOZ'_6$, $-(CH_2)_mSZ'_6$, $-(CH_2)_mCO_2Z'_6$, $-(CH_2)_mNZ'_6C(O)Z_8$, $-(CH_2)_mC(O)Z_8$, $-(CH_2)_mOC(O)Z_8$, $-O(CH_2)_mNZ'_6Z'_7$, $-OC(O)NZ'_6Z'_7$, $-OC(O)(CH_2)_mCO_2Z'_6$, $-OSO_2Z_7$, $-(CH_2)_mN(CH_3)(CH_2)_nNZ'_6Z'_7$, $-(CH_2)_mOC(O)NZ'_6Z'_7$, $-(CH_2)_mS(O)_qZ_{11}$, $-(CH_2)_mP(O)Z_{12}Z_{13}$, $-(CH_2)_2P(S)Z_{12}Z_{13}$, $-(CH_2)_mSiZ'_{11}Z'_{12}Z'_{13}$; or **ii**) $-(CH_2)_n[N=X]$,

-OC(O)[N=X], $-(CH_2)_mOC(O)[N=X]$, aryl or lower arylalkyl, each *independently*

or substituted ~~(i.e. substituted~~ ^{with 1 to 4 members (A)} ~~between once and four times on the aryl~~
~~group or the heterocycle or non-substituted in which the substituent is~~

~~lower alkyl, lower arylalkyl, halo, hydroxy, -OCF₃, nitro, amino, lower alkylamino, di(lower alkyl)amino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl or~~ **iii)** Z₃ and Z₄ or Z₄ and Z₅ form together a chain ~~with~~ ^{consist} 3 or 4 members in which the elements of the chain are selected from the group ~~consisted of~~ ^{consists of} by CH, CH₂, O, S, N or NZ₉;

- Z_7 is (A) represents a lower alkyl ^{unsubstituted or} radical optionally substituted by ^{at least} one or more halo radicals identical or different, or an aryl ^{unsubstituted or} optionally substituted by ^{at least} one or more lower alkyl radicals identical or different;
- Z_6 and Z_7 ^{are} represent, independently, (A) i) H, a lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl, lower haloalkyl, or ii) aryl or lower arylalkyl, each ^{unsubstituted or substituted on} substituted (i.e. substituted between once and four times ^{with 1 to 4 members selected from the group} on the aryl group) or non substituted in which the ^{consists of} substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy ^{and} or lower alkoxy lower alkyl;
- Z_8 is (A) represents i) H, a lower alkyl, lower hydroxyalkyl, amino, lower alkylamino, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy, lower alkoxy lower alkyl, ^{and} lower haloalkyl, or ii) aryl or lower arylalkyl, each ^{unsubstituted} substituted (i.e. substituted between once and four times on the aryl group) or non substituted, ^{with (A)} in which the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy ^{and} or lower alkoxy lower alkyl;
- Z_9 is (A) represents i) H, a lower alkyl, lower haloalkyl, or ii) aryl ^{unsubstituted or} or lower arylalkyl, each ^{with (A)} substituted or non substituted in which the substituent is lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy ^{and} or lower alkoxy lower alkyl;
- Z_{10} is (A) represents i) H, a lower alkyl, lower haloalkyl, lower alkoxy, or ii) aryl ^{unsubstituted or} substituted (i.e. having one to four substituents on the aryl group) or non substituted in which the substituent is lower alkyl, lower haloalkyl, lower hydroxyalkyl ^{and} or lower alkoxy lower alkyl;
- Z_{11} is (A) represents a lower alkyl, aryl, $-(CH_2)_mOZ_{14}$, $-(CH_2)_mSZ_{14}$, $-(CH_2)_2NZ_{14}Z_{15}$ ^{and} or $-(CH_2)_m[N=X]$;
- Z_{12} and Z_{13} ^{are} represent, independently, (A) i) a lower alkyl, aryl, lower alkoxy, aryloxy ^{and} or amino;
- Z'_{11} , Z'_{12} and Z'_{13} ^{are} represent, independently, H or a lower alkyl radical;
- Z_{14} and Z_{15} ^{are} represent, independently, (A) H, lower alkyl ^{and} or aryl;
- Z_{16} is represents H or $-OZ_{21}$;
- Z_{17} is represents $-OZ'_6$ or $-NZ'_6Z'_7$;
- Z_{18} and Z_{19} ^{are} represent, independently, (A) H, halo, lower alkyl, lower alkoxy ^{and} or hydroxy;
- Z_{20} is represents H or halo;

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Z_{21} is (A) represents H, ^{and} a lower alkyl, -CHO ^{or} -C(O)(CH₂)_mCH₃;
 Z_p is represents H or an easily cleavable group preferably chosen from the groups corresponding to the formula ~~C(O)-A-NZ₂₂Z₂₃~~, ^{where A} in which A ^{is} represents a linear or branched alkylene radical optionally substituted by a radical ^(A) chosen from the free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino, mono ~~and~~ dialkylamino radicals;
 Z_{22} and Z_{23} ^(A) represent, independently, H, a lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl, lower haloalkyl, or ⁽ⁱⁱ⁾ substituted or non substituted aryl or lower arylalkyl ^(or 2), substituted ^{1 to 4 members of the group consisting of} one to four times on the aryl group, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy ^{and} or lower alkoxy lower alkyl;
 m is an integer comprised between 0 and 6;
 n is 1 or 2; and
 q represents an integer from 0 to 2; and
 $[N=X]$ ^{is} represents a heterocyclic group with 4 to 7 ^{and 3} members with the nitrogen atom which is a member of the heterocyclic ring, and X ^{is} representing the chain necessary to complete said heterocyclic group and selected from the group ^{consisting of} O, S, CH₂, CH, N, NZ₉ and C(O)Z₁₀;

^{it is} or pharmaceutically acceptable salts of thereof.

2. ^{Compounds} of general formula (A₁) or (A₂) as claimed in claim 1, in racemic or enantiomeric form or any combinations of these forms, ^{wherein} characterized in that

Z_1 is (A) represents a lower alkyl, a lower alkenyl, a lower alkynyl, a lower haloalkyl, a lower alkoxy lower alkyl ^{and} or lower alkylthio lower alkyl;

Z_2 is (A) represents H, halo ^{and} or -OSO₂Z₇;

Z_3 , Z_4 and Z_5 represent, independently, ⁽ⁱ⁾ H, halo, lower haloalkyl, lower alkyl, lower alkenyl, cyano, lower cyanoalkyl, nitro, lower nitroalkyl, amido, lower amidoalkyl, hydrazino, lower hydrazinoalkyl, azido, lower azidoalkyl, -(CH₂)_mNZ'₆Z'₇, -(CH₂)_mOZ'₆, -(CH₂)_mSZ'₆, -(CH₂)_mCO₂Z'₆, -(CH₂)_mNZ'₆C(O)Z₈, -(CH₂)_mC(O)Z₈, -(CH₂)_mOC(O)Z₈, -O(CH₂)_mNZ'₆Z'₇, -OC(O)NZ'₆Z'₇, -OC(O)(CH₂)_mCO₂Z'₆, ^{and} -OSO₂Z₇ or ⁽ⁱⁱ⁾ -(CH₂)_n[N=X], -OC(O)[N=X], -(CH₂)_mOC(O)[N=X] ^{in which} [N=X], in this invention, represents a heterocyclic group with 4 to 7 ^{and 3} members with the nitrogen atom ^X, which is a member of the heterocyclic group, and X ^{is} represents the remaining members, which are

necessary to complete the heterocyclic group, selected from the group constituted by O, S, CH₂, CH, N, NZ₉ and COZ₁₀, aryl or lower arylalkyl, each substituted (i.e. substituted between once and four times on the aryl group or the heterocycle) or non substituted in which the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl or iii) Z₃ and Z₄ or Z₄ and Z₅ form together a chain with 3 or 4 members in which the elements of the chain are selected from the group constituted by CH, CH₂, O, S, N or NZ₉;

5 Z₆ is (A) represents i) H, halo, lower haloalkyl, alkyl containing 1 to 12 carbon atoms optionally substituted by one or more halo radicals identical or different, lower alkoxy, lower alkoxy lower alkyl, lower alkylthio lower alkyl, cycloalkyl, cycloalkyl lower alkyl, cyano, cyanoalkyl, lower alkyl lower sulphonylalkyl, lower hydroxyalkyl, nitro, -(CH₂)_mC(O)Z₈,
15 -(CH₂)_mNZ'₆C(O)Z₈, -(CH₂)_mNZ'₆Z'₇, -(CH₂)_mN(CH₃)(CH₂)_nNZ'₆Z'₇, -(CH₂)_mOC(O)Z₈, -(CH₂)_mOC(O)NZ'₆Z'₇, -(CH₂)_mS(O)_qZ₁₁, -(CH₂)_mP(O)Z₁₂Z₁₃, -(CH₂)₂P(S)Z₁₂Z₁₃, -(CH₂)_mSiZ'₁₁Z'₁₂Z'₁₃; or ii) -(CH₂)_n[N=X], -OC(O)[N=X], -(CH₂)_mOC(O)[N=X], each substituted (i.e. substituted between once and four times on the heteroaryl group) or non substituted in which the substituent is a lower alkyl, lower arylalkyl, halo, hydroxy, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl; or iii) aryl or lower arylalkyl, each substituted (i.e. substituted between once and four times on the aryl group) or non substituted in which the substituent is a lower alkyl, halo, hydroxy, nitro, -OCF₃, amino, lower alkylamino, di(lower alkyl)amino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl;

25 Z₇ is (A) represents a lower alkyl radical optionally substituted by one or more halo radicals identical or different, or an aryl optionally substituted by one or more lower alkyl radicals identical or different;

30 Z₆ and Z'₇ represent, independently, i) H, a lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl, lower haloalkyl, or ii) aryl or lower arylalkyl, each substituted (i.e. substituted between once and four times on the aryl group) or non substituted in which the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl;

- Z_8 is (A) represents i) H, a lower alkyl, lower hydroxyalkyl, amino, lower alkylamino, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy, lower alkoxy lower alkyl, lower haloalkyl, or ii) aryl or lower arylalkyl, each substituted (i.e. substituted between once and four times on the aryl group) or non-substituted, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl;
- Z_9 is (A) represents i) H, a lower alkyl, lower haloalkyl, or ii) aryl or lower arylalkyl, each substituted or non-substituted in which the substituent is lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl;
- Z_{10} is (A) represents i) H, a lower alkyl, lower haloalkyl, lower alkoxy, or ii) aryl substituted (i.e. having one to four substituents on the aryl group) or non-substituted in which the substituent is lower alkyl, lower haloalkyl, lower hydroxyalkyl or lower alkoxy lower alkyl;
- Z_{11} is (A) represents a lower alkyl, aryl, $-(CH_2)_mOZ_{14}$, $-(CH_2)_mSZ_{14}$, $-(CH_2)_2NZ_{14}Z_{15}$ or $-(CH_2)_m[N=X]$;
- Z_{12} and Z_{13} are represent, independently, a lower alkyl, aryl, lower alkoxy, aryloxy or amino;
- Z'_{11} , Z'_{12} and Z'_{13} are represent, independently, H or a lower alkyl radical;
- Z_{14} and Z_{15} are represent, independently, H, lower alkyl or aryl;
- Z_{16} is represents H or $-OZ_{21}$;
- Z_{17} is represents $-OZ'_6$ or $-NZ'_6Z'_7$;
- Z_{18} and Z_{19} are represent, independently, H, halo, lower alkyl, lower alkoxy or hydroxy;
- Z_{20} is represents H or halo;
- Z_{21} is represents H, a lower alkyl, $-CHO$ or $-C(O)(CH_2)_mCH_3$;
- Z_p represents H or an easily cleavable group preferably chosen from the groups corresponding to the formula $-C(O)-A-NZ_{22}Z_{23}$, in which A represents a linear or branched alkylene radical optionally substituted by a radical chosen from the free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino, mono or dialkylamino radicals;
- Z_{22} and Z_{23} are represent, independently, H, a lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl, lower haloalkyl, or ii) substituted or non-substituted aryl or lower arylalkyl (i.e. substituted by 1 to 4

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members of the group consists of
~~one to four times on the aryl group~~, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy ^{and} or lower alkoxy lower alkyl;

m is an integer ~~comprised~~ between 0 and 6;

5 n is 1 or 2; and

q ^{is} represents an integer from 0 to 2; and

[N=X] ^{is} represents a heterocyclic group with 4 to 7 ^{ring} members with the nitrogen atom which is a member of the heterocyclic ring, and X ^{is} representing the chain necessary to complete said heterocyclic group and ^{is} (selected from the group ~~constituted~~ ^{consisting of} by O, S, CH₂, CH, N, NZ₉ and COZ₁₀;

^a or pharmaceutically acceptable salts ~~of~~ thereof.

^{Ac} 3. ~~Compounds as claimed in claim 1 or 2, characterized in that Z₂ represents H or halo~~
~~or pharmaceutically acceptable salts of thereof.~~

^{Ac} 4. ~~Compounds as claimed in claim 1 or 2, characterized in that Z₃ represents halo ; or a~~
~~pharmaceutically acceptable salts of thereof.~~

^{Ac} 5. ~~Compounds as claimed in any of claims 1 to 4, characterized in that~~

Z₁ ^{is} represents a lower alkyl ;

Z₂ ^{is} represents H or halo ; (A)

20 Z₃, Z₄ and Z₅ ^{are} represent, independently, i) H, halo, lower alkyl, -(CH₂)_mNZ'₆Z'₇, -
 (CH₂)_mOZ'₆-OSO₂Z₇ or ii) -(CH₂)_n[N=X] or iii) Z₃ and Z₄ or Z₄ and
 Z₅ form together a chain with 3 or 4 members in which the elements of
 the chain are selected from the group ^{consisting of} by CH, CH₂, O, S, N
^{and} or NZ₉;

25 Z₆ ^{is} (A) represents i) H, halo, alkyl containing 1 to 12 carbon atoms ^{unsubstituted or} optionally
 substituted by ^{at least} one or more halo radicals identical or different, lower
 alkoxy lower alkyl, cycloalkyl, cycloalkyl lower alkyl, lower
 hydroxyalkyl, -(CH₂)_mNZ'₆Z'₇ ^{and} -(CH₂)_mSiZ'₁₁Z'₁₂Z'₁₃ ; or ii) -
 (CH₂)_n[N=X] ^{is} substituted or ~~non~~ substituted in which the substituent is
 a lower alkyl or lower arylalkyl or iii) aryl or lower arylalkyl, ^{unsubstituted or} each
 30 substituted or ~~non~~ substituted in which the substituent is a lower alkyl,
 halo, -OCF₃, di(lower alkyl)amino ^{and} or lower haloalkyl ;

Z₇ ^{is} represents a lower alkyl ^{unsubstituted or} optionally substituted by ^{at least} one or more
 halo radicals identical or different ;

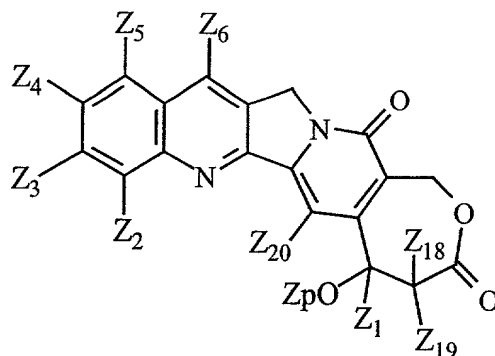
Z'₆ and Z'₇ ^{are} represent, independently, i) H, ^{or} lower alkyl, or ii) lower arylalkyl ;

35 Z₉ ^{is} represents a lower alkyl or lower arylalkyl ;

Z'₁₁, Z'₁₂ and Z'₁₃ ^{are} represent, independently, a lower alkyl radical ;

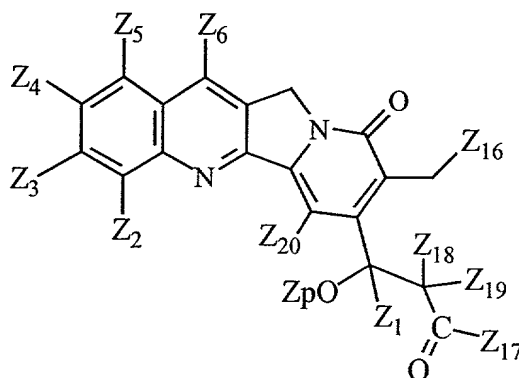
- ¹⁵
Z₁₆ represents H or -OZ₂₁;
- ¹⁵
Z₁₇ represents -OZ'₆ or -NZ'₆Z'₇;
- ^{are}
Z₁₈ and Z₁₉ represent, independently, H, ^{or} halo;
- ¹⁵
Z₂₀ represents H;
- 5 ¹⁵ ^(B) Z₂₁ represents H, a lower alkyl or -C(O)(CH₂)_mCH₃;
- ¹⁵
Z_p represents H or a group corresponding to the formula -C(O)-A-NZ₂₂Z₂₃, in which A represents a linear or branched alkylene ^{unsubstituted or} ^{by (B)} optionally substituted by a radical chosen from the free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino ^{and} mono ^{and} or dialkylamino radicals;
- 10 Z₂₂ and Z₂₃ represent, independently, H, ^{or} lower alkyl;
- m is an integer comprised between 0 and 6;
- n is 1 or 2; and
- ¹⁵
q represents an integer from 0 to 2; and
- 15 [N=X] represents a heterocyclic group with 4 to 7 ^{ring} members, X ^{is} representing the chain necessary to complete said heterocyclic group and ^{is} selected from the group ^{consisting of} O, CH₂, CH, N and NZ₉;
- ^{and a}
or pharmaceutically acceptable salts ~~of~~ thereof.
- ^A ^c
6. ^{wherein} Compounds as claimed in any of claims 1 to 5, characterized in that Z₁₈, Z₁₉ and Z₂₀ ^{are} represent H; or pharmaceutically acceptable salts ~~of~~ thereof.
- 20 ^A ^c
7. ^{wherein} Compounds as claimed in any of claims 1 to 6, characterized in that Z₁ ^{is} represents ethyl ^{and a} or pharmaceutically acceptable salts ~~of~~ thereof.
- ^A ^c ^{of claim} ^{wherein}
8. Compounds as claimed in claim 1 or 2, characterized in that Z_p ^{is} represents a group corresponding to the formula -C(O)-A-NZ₂₂Z₂₃ ^{and a} or pharmaceutically acceptable salts ~~of~~ thereof.
- 25 ^A ^c
9. ^{of} Compounds as claimed in claim 1 or 2, characterized in that Z_p ^{is} represents H ^{and a} or pharmaceutically acceptable salts ~~of~~ thereof.
- ^A ^c ^{of} ^{having}
10. Compounds as claimed in claim 1 or 2, characterized in that they correspond to the formula (A1)

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wherein Z_1 , Z_2 , Z_3 , Z_4 , Z_5 , Z_6 , Z_{18} , Z_{19} , Z_{20} and Z_p are as defined in claim 1 ^{and a} ~~or~~ pharmaceutically acceptable salts ~~of~~ thereof.

11. ^{Ac} ~~Compounds as claimed in claim 1 or 2, characterized in that they correspond to the formula (A2)~~ ^{having}



wherein Z_1 , Z_2 , Z_3 , Z_4 , Z_5 , Z_6 , Z_{16} , Z_{17} , Z_{18} , Z_{19} , Z_{20} and Z_p are as defined in claim 1 ^{and a} ~~or~~ pharmaceutically acceptable salts ~~of~~ thereof.

12. ^{Ac} ~~Compounds as claimed in claim 1 or 2, characterized in that Z_6 represents $-(CH_2)_mSiZ'_{11}Z'_{12}Z'_{13}$ ^{and a} ~~or~~ pharmaceutically acceptable salts ~~of~~ thereof.~~ ^{wherein}

13. ~~Compounds as claimed in claim 12, characterized in that they correspond to the following formula :~~ ^{if compound of claim 1 selected from the group consists of}

(5R)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1H,3H-oxepino[3',4':6,7]indolizino [1,2-b] quinoline-3,15-dione ~~and~~

15 (5R)-5-ethyl-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1H,3H-oxepino [3',4':6,7]indolizino [1,2-b] quinoline-3,15-dione ;

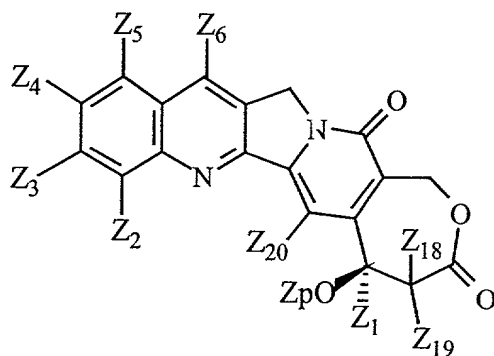
14. ^{Ac} ~~Compounds as claimed in claim 1 or 2, characterized in that Z_2 represents H or halo, Z_3 represents halo, Z_4 represents H, halo ^{or} lower alkyl, Z_5 represents H or halo, and Z_6 represents H, lower alkyl ^{or} $-(CH_2)_n[N=X]$ substituted in which the substituent ^{is} ~~is a~~ lower alkyl ^{and a} ~~or~~ pharmaceutically acceptable salts ~~of~~ thereof.~~ ^{wherein}

A compound of claim 1 selected from the group consisting of
 15. ~~Compounds as claimed in claim 14, characterized in that they correspond to the following formula:~~

(5R)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1H,3H-oxepino [3',4':6,7] indolizino [1,2-b] quinoline-3,15-dione *and*

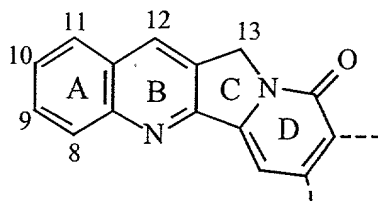
- 5 (5R)-5-ethyl-9,11-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1H,3H-oxepino [3',4':6,7] indolizino [1,2-b] quinoline-3,15-dione ; or pharmaceutically acceptable salts of thereof.

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 16.) ~~Compounds as claimed in claim 1 or 2, characterized in that they correspond to the formula~~

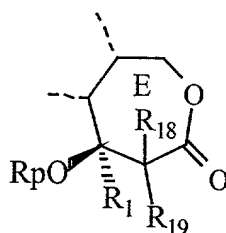


10 wherein Z₁, Z₂, Z₃, Z₄, Z₅, Z₆, Z₁₈, Z₁₉, Z₂₀ and Z_p are as defined in claim 1 *and a* ~~for~~ pharmaceutically acceptable salts ~~of~~ thereof.

17. A method of treating cancer in warm-blooded animals comprising administering to warm-blooded animals in need thereof a camptothecin analog characterized in that
 15 said analog is a [A,B,C,D,E] pentacyclic compound, the cycles [A,B,C,D]



comprising any substitution on the various sites available for substitution(s), and the [E] cycle being a 7-ring member β -hydroxy lactone ring of the formula



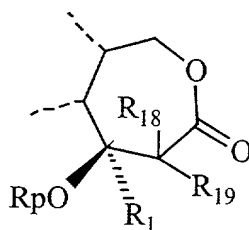
wherein R_1 is selected from the group consisting of alkyl of 1 to 6 carbon atoms, alkenyl and alkynyl of 2 to 6 carbon atoms, haloalkyl of 1 to 6 carbon atoms, alkoxyalkyl of 2 to 12 carbon atoms and alkylthioalkyl of 2 to 12 carbon atoms, R_p is hydrogen or an easily cleavable group, R_{18} and R_{19} are individually selected from the group consisting of hydrogen, halogen, OH and alkyl and alkoxy of 1 to 6 carbon atoms and its non-toxic, pharmaceutically acceptable salts.

18. A method of treating cancer according to claim 17, the cycles [A,B,C,D] comprising any substitution on the sites 8, 9, 10, 11, 12 or 13.

19. A method of treating cancer according to claim 17, the cycles [A,B,C,D] comprising any substitution on the sites 8, 9, 10, 11 or 12.

20. A method of treating cancer according to claim 17, the cycles [A,B,C,D] comprising any substitution on the sites 9, 10, 11 or 12.

21. A method of treating cancer in warm-blooded animals comprising administering to warm-blooded animals in need thereof a camptothecin having 5 rings with a 7-ring member β -hydroxy lactone ring of the formula



wherein R_1 is selected from the group consisting of alkyl of 1 to 6 carbon atoms, alkenyl and alkynyl of 2 to 6 carbon atoms, haloalkyl of 1 to 6 carbon atoms, alkoxy alkyl of 2 to 12 carbon atoms and alkylthioalkyl of 2 to 12 carbon atoms, R_p is hydrogen or an easily cleavable group, R_{18} and R_{19} are individually selected from the group consisting of hydrogen, halogen, OH and alkyl and alkoxy of 1 to 6 carbon atoms and its non-toxic, pharmaceutically acceptable salts.

22. A method of treating cancer as claimed in claim 17 ~~or 21, characterized in that~~ ^{wherein the} cancer is selected from the group consisting of leukemia, colon cancer, lung cancer, prostate cancer, breast cancer, melanoma, ovarian cancer and gastric cancer.

23. A method of treating cancer as claimed in claim 22, ~~characterized in that~~ ^{wherein the} cancer is selected from the group consisting of leukemia, colon cancer, lung cancer, prostate cancer and breast cancer.

24. A method ~~as claimed in any of claims 17 to 23~~ ^{wherein} characterized in that R₁₈ and R₁₉ are hydrogen.

25. A method ~~as claimed in any of claims 17 to 24~~ ^{wherein} characterized in that R_p is hydrogen.

26. A method ~~as claimed in any of claims 17 to 25~~ ^{wherein} characterized in that R₁ is ethyl.

27. A method ~~as claimed in any of claims 17 to 26~~ ^{wherein the} characterized in that camptothecin analog is selected from ~~the group consisting of~~

(5R)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1H,3H-oxepino [3',4':6,7] indolizino [1,2-b] quinoline-3,15-dione ;

(5R)-1-[9-chloro-5-ethyl-5-hydroxy-10-methyl-3,15-dioxo-4,5,13,15-tetrahydro 1H,3H-oxepino [3',4':6,7] indolizino [1,2-b] quinolin-12-yl-methyl]-4-methyl-hexahydropyridium chloride ;

(5R)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1H,3H-oxepino [3',4':6,7] indolizino [1,2-b] quinoline-3,15-dione ~~and~~

(5R)-5-ethyl-9,11-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1H,3H-oxepino [3',4':6,7] indolizino [1,2-b] quinoline-3,15-dione ~~or its~~ ^a pharmaceutically acceptable salt thereof.